Hidden Potential

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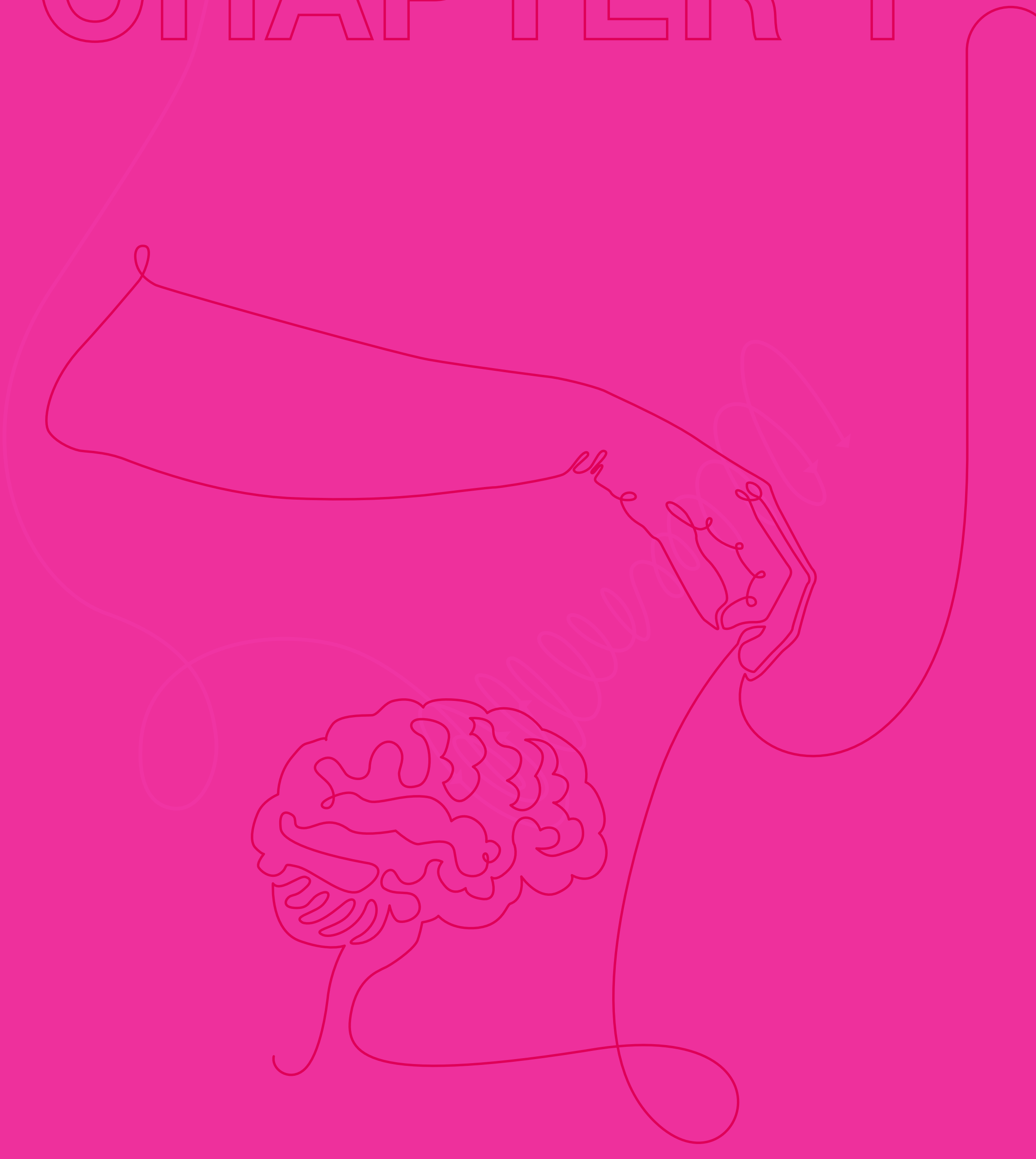
CHAPTER 1

introduction



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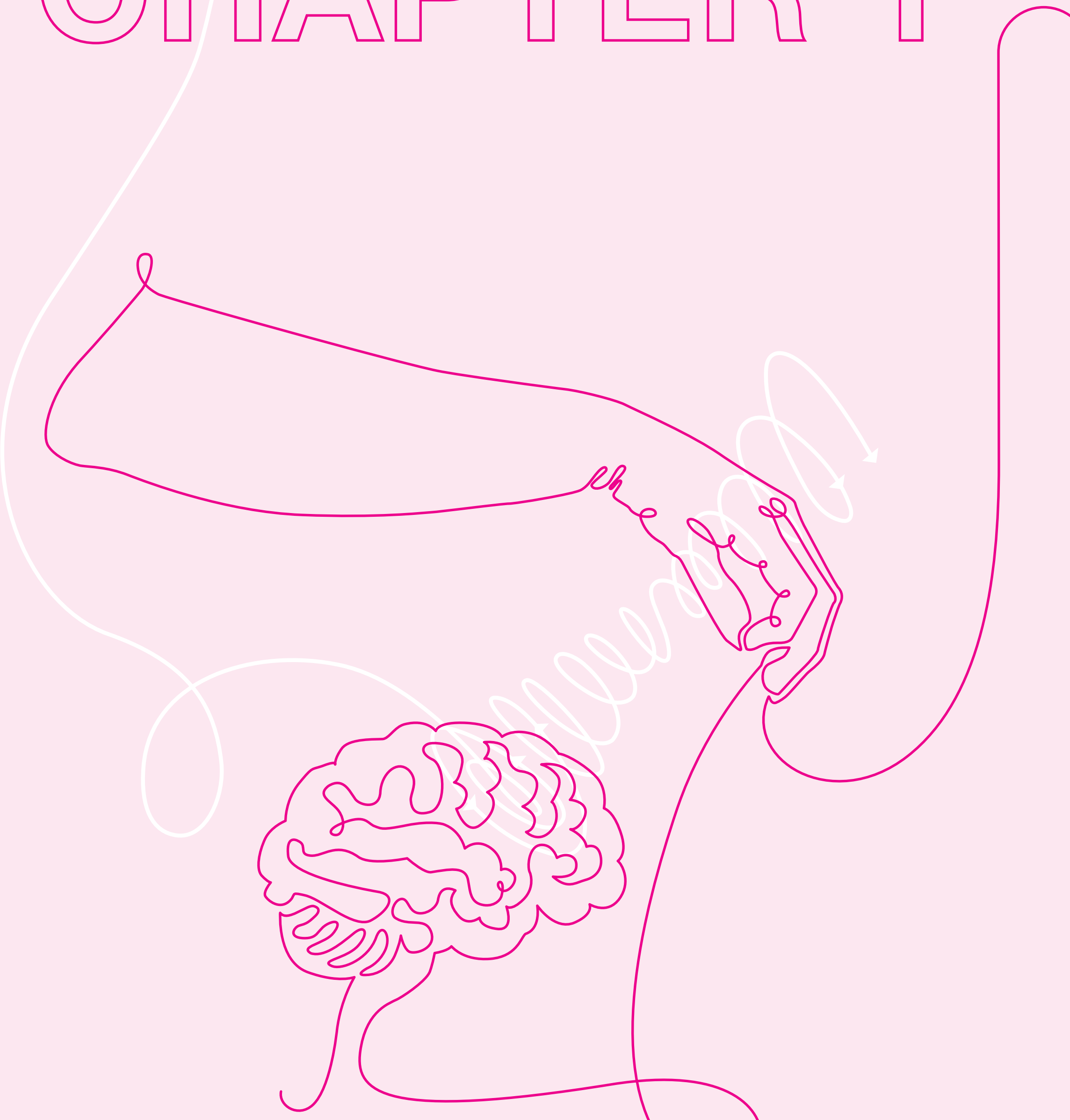

INTRODUCTION

STROKE

The word 'stroke' has many meanings. It is common to use the expression 'a stroke of luck' which is a pleasant surprise. However, most people who have experienced the consequences of the medical condition called 'stroke' would rather associate it with substantial misfortune. The word stroke denotes a caress of a loved one's hand, and at the same time embodies the violence that Hippocrates referred to when he wrote the first definition of a stroke in around 400 BC. He called it apoplexy, which literally translates to 'struck down by violence'.[1] The unexpected onset of symptoms with far-reaching repercussions for daily life does indeed show resemblance to the suddenness of a violent stroke.
The exact definition of the medical term 'stroke' is subject for discussion.[2] In essence, it involves an interruption of blood supply to a part of the brain.[3] When regional brain blood supply is arrested and the cells are deprived of oxygen, they lose function within minutes and eventually cell death occurs. The cause of blood shortage can be either ischemia or hemorrhage. Ischemia is most often caused by an obstruction, for instance a clot, of a supplying blood vessel. A hemorrhage is a massive local bleeding, for instance due to tearing of a blood vessel, that by pressure blocks oxygen-rich blood from entering the affected brain area.[3–5] Symptoms of stroke depend on the brain region that is involved. Specific functions like movement, coordination, speech and attention are controlled by networks with regional concentration of neural activity. When such a region is affected, the corresponding function is impaired. If the flow of oxygen returns in time, damage to a part of the neural network may be reversible. It will survive, but needs some time to regain normal function. Such a region where cell damage is not permanent, is called penumbra. The penumbra, together with unaffected brain regions within the network that have the potential to take over lost function, offers a focus for recovery (Fig. 1.1).

Stroke is among the leading causes of disabilities and restrictions of participation in society. The World Health Organization estimates that worldwide, 15 million people suffer a stroke per year.[6] The incidence varies between countries but, overall, it increases with age. The Disability Adjusted Life Years (DALY) score is a measure of the impact of a condition on society in terms of healthy life years lost. In 2015 it was second highest for stroke in the Netherlands (after coronary heart disease). The burden of stroke is this large because stroke survivors often endure disabilities that hinder independence in activities of daily living. In 1994, Nakayama

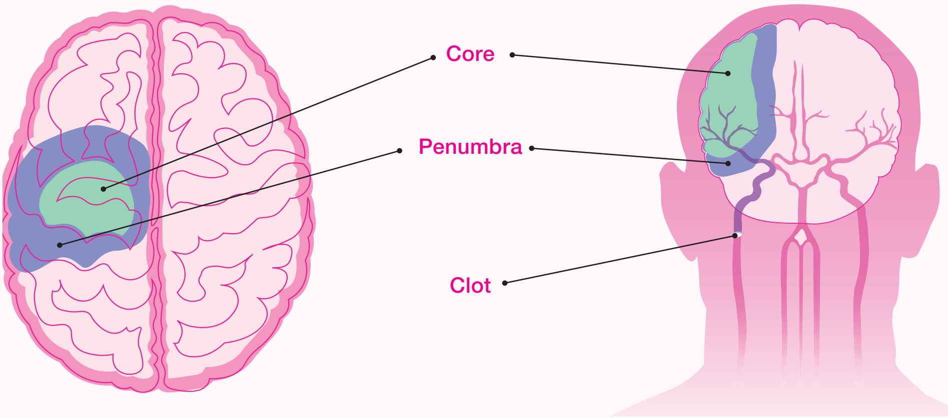

FIGURE 1.1. *Schematic representation of the brain areas involved in a stroke. The clot obstructs blood flow to a specific brain area, the core of which is irreversibly damaged. The penumbra is the region that is affected in the acute phase, but may regain function if timely restoration of blood flow takes place.*

and co-workers estimated that a third of stroke patients suffers a paresis of the upper extremity.[7] Given the importance of hand function for activities of daily living, a paresis of the upper extremity has important consequences for participation. Indeed, Skolarus and co-workers established that stroke survivors experience many types of restrictions for participation in social activities, more than they expected based on sociodemographic status and comorbidities.[8] Rehabilitation treatment has the purpose to let patients regain their social role and a sense of control over their life.[9]

REHABILITATION TREATMENT AND MECHANISMS IN RECOVERY

Rehabilitation is typically organized following the International Classification of Functioning (ICF).[10] This is a model of the interaction between individuals, their health condition and their context. In this framework, the human functioning is divided in three levels. The first level concerns *body function* and represents physiological functions of body systems. It also includes body structures, such as organs and limbs. Examples of this level are signal conduction in the nervous system and the structural integrity of a limb, for instance the hand after amputation. The second level is *activity*, where examples would be walking, grasping and speaking. The third level is *participation*, which implies interaction with the environment and in particular society. For each level, the potential capacity of the individual is scored, alongside the actual performance in a given situation.

Rehabilitation aims at decreasing the difference between these two qualifications. Rehabilitation interventions after stroke focus on both restorative and compensatory mechanisms. Restorative mechanisms require the restitution of function of damaged or functionally depressed brain areas in stroke.[11,12] Therefore, they are primarily associated with the above two levels of body function and activity in ICF. Interventions that are based on compensatory strategies may relate to all three ICF levels of body function. Compensation may take place at the structural level, where intact brain cells within the network may take over functions of damaged brain cells. Compensation can also occur at the level of activity. For instance, body parts can be moved in a different way to accomplish the same result: even the contralateral body half may be involved. Ultimately, assistive devices are often associated with rehabilitation and generally serve for compensatory strategies to facilitate participation. Compensation as a focus of rehabilitation treatment is less dependent on natural recovery processes, but on the downside also fails the opportunity to enhance these processes.

A general working mechanism in the brain is neuroplasticity. It plays an important role in learning. It encompasses the processes in which the strength of synaptic connections adjusts in response to either environmental stimuli or alterations in synaptic activity in a network.[13] As such, every brain is constantly evolving on a neuronal level. The synapse changes can either be facilitatory, with the result that an impulse is amplified, or inhibitory, as part of a feedback mechanism that serves to fine-tune the neural interactions. The question remains whether the changes that are measured at a neuronal level after stroke relate to skill acquisition, and thus if they are part of restoration or compensation.[14] This is relevant for timing of therapy types. In the first weeks after stroke, it is assumed that the penumbra regains function. In order to restore as much function as possible to the original structures, rehabilitation in this phase first focuses on optimal stimulation of the penumbra. Secondary, compensation at body function level, and eventually at the other levels, is targeted. If techniques make it possible to define which category of neuroplastic processes take place, treatment could be adjusted to the actual potential for recovery of the individual patient.

Another facet that complicates therapy planning is the way in which the many possible symptoms of stroke interact. For instance, many patients experience fatigue and cognitive problems. Engaging in intensive treatment protocols may be too demanding for these patients. It is therefore important to adjust the content and intensity of the treatment to the capacity of the individual, both in terms of how much recovery is expected and of how much therapy of a certain kind a patient can endure. Adequate and early prediction of individual possibilities and impossibilities of each stroke patient is paramount for an appropriate content and intensity of therapy.

Several prediction models were developed to guide health workers. The majority of patients with mild to moderate arm/hand impairments after stroke display a proportional motor recovery of an estimated 70% of maximal potential recovery. This was described in the proportional recovery model.[15,16] Nijland and co-workers demonstrated the predictive capacity of finger extension in combination with shoulder abduction, when assessed in the acute phase after stroke.[17] This finding led to one of the components for the so-called PREP and PREP2 algorithms, in which finger extension and shoulder abduction are coupled to functional MRI and Transcranial Magnetic Stimulation (TMS, see below). The combination of methods is supposed to lead to more accurate prediction of motor outcome after stroke.[18,19] However, up to now it has been a challenge to determine which patients will improve according to the prediction models and which will not. Simply said, we are not yet able to predict in our individual paretic stroke patients whether their hand will ever move normally again.

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

TMS is a technique that can provide information about electrical conduction through the nervous system. It is based on the principle of magnetic induction (Fig. 1.2). A change of electrical current in a coil is applied to create a short magnetic field. This field penetrates tissues such as skin and is also hardly influenced by the bone of the skull as would happen when using direct electric current.[20]

The magnetic field subsequently activates neurons to discharge which creates propagating electrical impulses. The field can be aimed at specific brain regions that are coupled to function and anatomy, such as the motor cortex that coordinates movement, and its innermost part that links to leg muscles. When the motor cortex is stimulated by TMS, many motor neurons are simultaneously activated. Their activity is passed to the motoneurons in the spinal cord and beyond and eventually causes discharge and contraction of motor units in the muscle. The summed simultaneous motor unit activity can be measured by surface electromyography (sEMG) using skin electrodes over the muscle. A motor evoked potential (MEP) is picked up by the surface electrodes. It typically consists of a negative deflection from the baseline activity (conventionally represented upwards

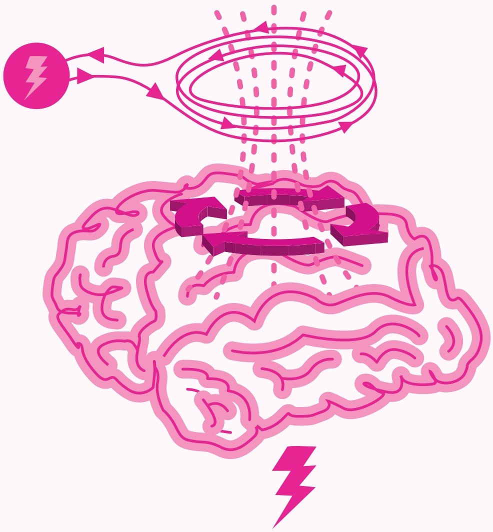

FIGURE 1.2. *Magnetic induction and the shape of the magnetic field of a circular TMS coil.*

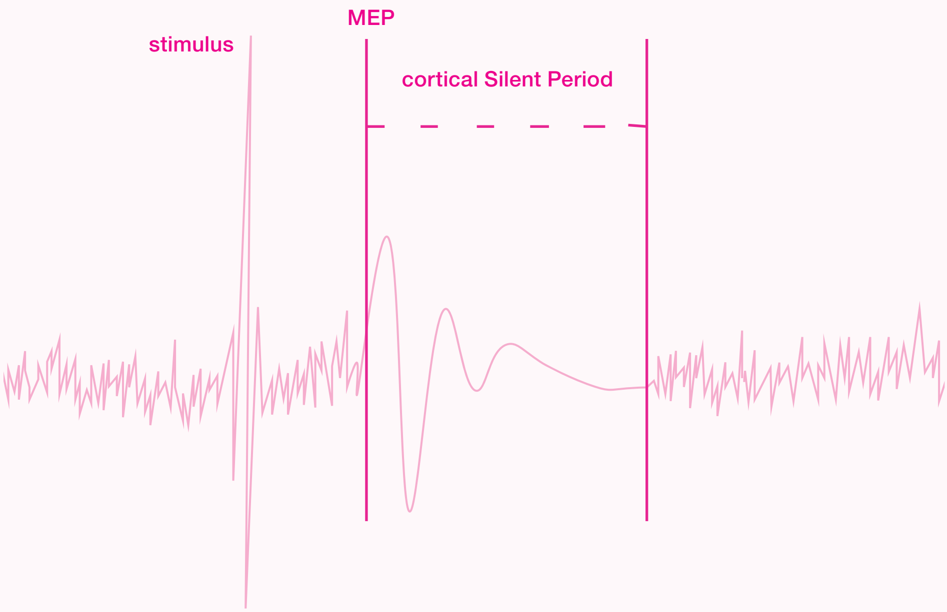

FIGURE 1.3. *A simplified example of an sEMG recording showing baseline EMG activity and a large negative-positive MEP, followed by an SP and restoration of the baseline EMG.*

in electrophysiological recordings, Fig. 1.3), followed by a positive deflection. When a muscle is pre-activated ('facilitated') by isometric contraction, there is a period directly after the MEP during which the activity in the muscle is fully suppressed, the so-called silent period (SP). The latency of the MEP reflects the conduction velocity over the full tract that the electrical current traverses between motor cortex and muscle. The amplitude of the MEP provides information about the number of motor neurons involved. It depends on the intensity of the stimulus, hence the smallest threshold intensity where a MEP can be evoked is complementary to the amplitude of the MEP. The relation between physiological phenomena and the SP as a variable is more complex. The inhibition of baseline muscle activity is assumed to be mediated by cortical inhibitory interneurons in the first part of the SP, and by spinal interneurons in the latter part.[21]

A phenomenon that has to be considered in TMS more than in peripheral electrical stimulation is crosstalk in the EMG assessment. This refers to the electrical activity recorded as a result of electrical discharges in more muscles than only the targeted one. The crosstalk might be large because by cortical stimulation, and thus involvement of more interneurons, TMS typically stimulates many motor neurons. This leads to simultaneous muscle activity in a larger area of agonist and antagonist muscle groups.

TMS is one of the modalities that have been applied to make predictions of recovery after stroke. Its advantage over clinical tests is that the ICF level of body function can be measured more directly, and that active cooperation of the patient is not required. This can be helpful when a patient is unable to follow instructions, for example due to aphasia, impaired consciousness or cognitive deficits. In these cases, with TMS it is still possible to assess neural conduction and the potential of the corticospinal tract to retain or regain function. The TMS variable that has the strongest association to long term arm and hand recovery is the presence of a MEP in an arm or hand muscle.[22–25] In their meta-analysis, Coupar and co-workers calculated a significant odds ratio of 11.76 for some recovery when a MEP is present in an upper extremity muscle.[25]

Another variable that may be relevant for prediction of hand function after stroke is the SP. Because this variable depends on the integrity of both the corticospinal tracts and the motor cortex, theoretically it can provide information about both structures. This is a potential benefit of the variable. However, it requires deep understanding of the processes involved to be able to correctly interpret the outcomes. The downside of this variable is that it depends on the presence of a voluntary muscle contraction, whereas one of the advantages of TMS as such over clinical tests is that it does not require muscle pre-activation. In addition, SP outcomes after stroke have shown to be heterogeneous, for which time after stroke appears to be an important explanation. Therefore, the silent period possibly represents processes of recovery of function instead of being a stable factor throughout time, and its assessment may need to be repeated.[21]

While there is ample evidence about the variables that are most informative for prediction after stroke, there is little consensus on which specific upper limb muscles should be targeted. Most studies focus on either distal intrinsic hand muscles such as the abductor digiti minimi and first digital interosseus muscles, or large proximal muscles such as the biceps brachii and deltoid muscles.[24–26] With the rationale that distal muscles are more selectively connected to brain areas than proximal muscles, it seems appropriate to focus on hand muscles. However, these muscles are small and it can be a challenge to identify a target muscle properly. As a consequence, the muscles of the forearm are relatively underrepresented in the literature on prediction with TMS after stroke.

Systematic analysis of the studies of TMS variables as predictors of motor function after stroke is complicated because of the diversity of variables, the measurement set-up and the timing after stroke. Several reviews describe the heterogeneity of included studies as the main impediment to draw clinically relevant conclusions.[23–25,27]

OUTLINE OF THIS THESIS

The objective of the research underlying this thesis was to further explore which TMS outcome variables are suitable for an accurate prognostication and follow-up of upper extremity motor function after stroke.

PART 1: SILENT PERIOD DEFINITION

With regard to diversity of variables, not only the multitude of variables that can be measured is problematic, but also the diverse ways in which specific variables are defined. Particularly for the SP, several definitions have been described.[28–30] Theoretically, it is the period between the end of the MEP and the return to the EMG signal as it was before the stimulus. However, in practice, especially the end of the SP is difficult to assess. Sometimes there is a bout of EMG activity in the middle of what appears to be a SP, and sometimes there is a gradual increase of activity which makes the exact end point an approximation. For a variable to serve as a clinically relevant and feasible predictor, it is crucial to eliminate all possible sources for ambiguity. In the optimal situation, a measurement can be performed by different observers and lead to the same outcome, regardless of level of expertise. In the first part of this thesis, the focus is on how to define SP to optimize this variable for clinical application. *Chapter 2* explores whether stimulus-response characteristics of the SP as a function of increasing stimulus intensity depend on definition of the SP cutoff points. *Chapter 3* concerns the effect of SP definition on inter-observer agreement.

PART 2: MEP-VARIABLES OF FOREARM EXTENSOR MUSCLES

In studies on TMS variables for prediction after stroke, another aspect of heterogeneity is formed by the diversity of muscles that are studied. We encountered over 10 different muscles in separate study set-ups. The muscles that mostly appear in studies are the first dorsal interosseus (FDI), the abductor pollicis brevis (APB), the abductor digiti minimi (ADM) and the biceps brachii (BB).[24,27] Indeed, in terms of practicability of the measurements, the anatomy of these muscles enables easier localization for sEMG electrode placement and their function can be tested relatively isolated.[31,32]

However, from research on clinical predictors for recovery after stroke, finger extension and shoulder abduction stand out as most informative.[17] In addition, one of the shortcomings of MEP status is its limited negative predictive value, implying that MEP absence does not exclude recovery.[33] The second part of this thesis explores finger and wrist extensor muscle groups as possible targets for prognostic TMS studies. In *Chapter 4*, the feasibility of selective forearm muscle TMS measurements is addressed in a single healthy subject using multi-channel sEMG. *Chapter 5* further elaborates on this approach in a group of healthy subjects. *Chapter 6* is the only chapter in this thesis where stroke patients were studied: for the other chapters, healthy participants were included. In this chapter the added prognostic value of MEP amplitude of the extensor digitorum communis (EDC) muscle to clinical tests in the subacute phase after stroke is evaluated.